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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/470,168	12/22/1999	Mathew Grant Boston	GC538-2	5850

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GENENCOR INTERNATIONAL, INC.
925 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	27

DATE MAILED: 01/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/470,168	BOSTON ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-75 and 80-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-75,80-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed November 6, 2002 amending claims 69, 75 and 80, canceling claims 15, 16, 18, 20-28, 30-51, 58-62 and 77-79 and adding claims 83-100 has been entered.

Claims 63-75 and 80-100 are pending.

Claim Objections

Claims 64 and 74 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 64 and 74 recite "the oxidized form of said co-factor is NAD^+ or $NADP^+$ and said reduced form of said co-factor is NADH or NADPH". Claims 64 and 74 depend from claims 63 and 73, respectively. Claims 63 and 73 recite "the oxidized form of said co-factor is $NADP^+$ or NAD^+". The reduced forms of NAD^+ and $NADP^+$ are NADH and NADPH, respectively. Therefore, the recitation of the reduced forms in dependent claims does not limit the independent claims.

Applicant is advised that should claims 69 and 70 be found allowable, claims 98 and 99, respectively, will be objected to under 37 CFR 1.75 as being a substantial

duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 84 is objected to because of the following informalities: "T. acidophilum" should be spelled out as "*Thermophlasma acidophilum*". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 99 and 100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 99 recites the limitation "said recombinant host cells" (emphasis added). There is insufficient antecedent basis for this limitation in the claim.

Claim 100 recites "cells are modified to include a heterologous glucose dehydrogenase". Cells can be modified in different ways the metes and bounds of which are not defined. Amending the claim to recite "the host cells transformed with a

DNA encoding a heterologous glucose dehydrogenase", for example, would obviated this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 63-69, 71-74, 80-94, 96-98 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Light et al. in view of Kulbe et al.

Light et al. (US Patent 4,758,514) teach the pathway glucose - 2-KLG identical to steps a)-d) recited in independent claims 63, 73 and 80 (column 1, lines 16-29, and column 2, Reaction Scheme 1). They teach that glucose dehydrogenase activity is produced by many prokaryotic microorganisms (column 3, lines 57-62). Light et al. further teach the production of 2-KLG from glucose by an *Erwinia herbicola* (ATCC 21998) host cell transformed with 2,5-DKG reductase gene from *Cornybacterium* sp. ATCC 31090 (column 17, line 62 through column 20, line 5, Examples 5 and 6). This process comprises enzymatic oxidation of glucose by *Erwinia* glucose dehydrogenase into DKG and enzymatic reduction of DKG to 2-KLG. Light et al. teach that the enzymes can be used as cells producing thereof, in solution and in immobilized form (e.g.,

column 1, line 66, through column 2, line 26; column 3, lines 41-61; column 7, lines 44-46).

Kulbe et al. (WO 86/04353 cited on form PTO-892 mailed May 1, 2002) teach process for the intrasequential cofactor regeneration in enzymatic synthesis with one or plurality of steps. Two enzymes presenting the same specificity as to cofactor are used for the associated oxidation and reduction processes (abstract, Figures 4, 7 and 8). They teach that this process is particularly well adapted for the production of vitamin C, intermediate products thereof or precursors thereof and illustrate the production of 2-KLG from D-gluconic acid using three oxidative and one reductive steps wherein NADP and NADPH are recycled (abstract, Figure 8, for example). They teach that this process can be operated continuously, uses inexpensive substrates which are completely converted and provides high yields of very pure products. It is less polluting and cheaper.

It would have been obvious to the one of ordinary skill in the art at the time the invention was made to employ known oxidative and reductive enzymes to produce 2-KLG according to Reaction Scheme 1 taught by Light et al. and at the same time to recycle the cofactor choosing oxidases and reductases using oxidized and reduced forms of the same co-factor as taught by Kulbe et al.

Since enzymes involved in oxidation of glucose to DKG are known in the art, it would have been obvious to the one of ordinary skill in the art at the time the invention

was made to carry out non-fermentative oxidation of glucose into DKG using purified enzymes such as commercially available *T. acidophilum* glucose dehydrogenase (Sigma) or cells transformed with a DNA encoding a heterologous enzyme. As a matter of choice, the endogenous GDH can be mutated to increase the expression of GDH or its activity can be eliminated and a heterologous GDH activity can be introduced. One would have been motivated to use non-fermentative oxidation of glucose into DKG because it allows a more efficient and convenient production of larger quantities of DKG and KDG compared with the fermentative production. In particular, host cells of the family *Enterobacteriaceae* are suitable because they are known to produce the requisite enzymes. Some genera of the family *Enterobacteriaceae* such as *Erwinia* are known to produce the requisite enzymes, *supra*. Further, 2,5-DKG reductase can be introduced into such cells by various means known in the art to produce 2-KLG.

Furthermore, the cofactor regeneration can be incorporated into the process according to the teachings of Kulbe et al. who provide the motivation and a reasonable expectation of success that cofactor regeneration can be applied to the process for the production of the intermediate products of the vitamin C synthesis.

As a matter of choice the process can be continuous or batch employing soluble or immobilized enzymes or cells/membranes producing the requisite enzymes and can be carried out in the environment comprising various organic solvents and long polymers.

Claims 63-69, 71-74, 80-94, 96-98 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powers et al. in view of Kulbe et al.

Powers et al. (US Patent 5,795,761) teach the pathway glucose - 2-KLG. They further teach that a number of microorganisms such as *Erwinia*, *Acetobacter* and *Gluconobacter* can produce 2,5-DKG from glucose and the second group can reduce 2,5-DKG to 2-KLG (column 1, lines 25-61). They teach *Cornybacterium* reductase A:F22Y/A272G mutant having improved ability to catalyze conversion of 2,5-DKG to 2-KLG (Figure 10, claim 6, for example). Since enzymes involved in oxidation of glucose to DKG are known in the art it would have been obvious to the one of ordinary skill in the art at the time the invention was made to carry out non-fermentative oxidation of glucose into DKG using purified enzymes or cells transformed with a DNA encoding an enzyme. One would have been motivated to use non-fermentative oxidation of glucose into DKG because it allows a more efficient and convenient production of larger quantities of DKG and KDG compared with the fermentative production. In particular, host cells of the family *Enterobacteriaceae* are suitable because the methodology is greatly advanced as applied to said cells. Furthermore, they are also known to produce the requisite enzymes.

The teachings of Kulbe et al. are outlined above. It would have been obvious to the one of ordinary skill in the art at the time the invention was made to employ known oxidative and reductive enzymes to produce 2-KLG from glucose according to the

reactions taught by Powers et al. and at the same time to recycle the cofactor choosing oxidases and reductases using oxidized and reduced forms of the same co-factor as taught by Kulbe et al. The same explanation as provided in the preceding rejection is repeated herein.

Claims 69, 70, 75, 94, 95, 98 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Light et al. in view of Kulbe et al. and further in view of Cha et al.

The teachings of Light et al. and Kulbe et al. are outlined above.

Cha et al. (cited on form PTO-892 mailed May 1, 2002) isolated a *Pantoea citrea* gene encoding glucose dehydrogenase. The teach inactive mutants of said gene (page 72, Table 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to choose a *Pantoea citrea* host cell among *Enterobacteriaceae* host cells because the *Pantoea citrea* gene encoding GDH has been isolated and sequenced by Cha et al. allowing convenient genetic manipulation of said gene including its inactivation.

Claims 69, 70, 75, 94, 95, 98 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powers et al. in view of Kulbe et al. and further in view of Cha et al.

The teachings of Powers et al., Kulbe et al. and Cha et al. are outlined above.

It would have been obvious to the one of ordinary skill in the art at the time the invention was made to choose a *Pantoea citrea* host cell among *Enterobacteriaceae* host cells because the *Pantoea citrea* gene encoding GDH has been isolated and sequenced by Cha et al. allowing convenient genetic manipulation of said gene including its inactivation.

Response to Arguments

Applicant's arguments filed November 6, 2002 have been fully considered but they are not persuasive.

With regard to the 103(a) rejection, Applicants argue that "Light et al. concerned with in vivo process" (Remarks, page 7). This is not agreed with because the teachings of Light et al. are not confined to the working examples described therein. Furthermore, the working examples describe the process using transformed cells which is an *in vitro* process.

Applicants argue that a recycling of the co-factor is a critical element of the instant invention (page 7). However, the recycling of the co-factor using two enzymes

with the same specificity is disclosed by Kulbe et al., *supra*. Moreover, Kulbe et al. specifically teach that this process is particularly well adapted for the production of vitamin C, intermediate products thereof or precursors thereof, providing the requisite motivation and expectation of success.

Applicants argue that Kulbe et al. do not teach the exact steps recited in the independent claims (page 8). However, as a secondary reference in the 103(a) rejection, the Kulbe et al. reference does not have to disclose the same invention but only to make it obvious. In this case, Kulbe et al. definitely suggest regenerating cofactor in the production of vitamin C intermediates.

Applicants argue that there is no teaching or suggestion in the Powers et al. reference concerning recycling of cofactor (page 8). Examiner notes that the Powers et al. reference is applied under 103(a) not 102 and does not need to disclose all elements of the instant invention. As discussed above the suggestion for cofactor regeneration is provided by Kulbe et al.

Applicants further argue with regard to the Cha et al. reference that independent claim 63 is patentable over the cited references (page 9). This is not persuasive because the Cha et al. reference is not used in the rejection of claim 63. In fact, claim 63 does not recite a *Pantoea citrea* host cell.

In conclusion, the pathway for the production of 2-KLG is known in the art. The art does not disclose this pathway in conjunction with the cofactor recycling. However,

such recycling is suggested by the prior art rendering the invention as claimed obvious. Thus, the invention as claimed is not drawn to unexpected results but to the processes that are obvious over the prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is

(703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

January 23, 2003